(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 339 485 B1**

# (12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **31.03.93** (51) Int. Cl.5: **A61K 31/47**, //C07D215/52

(21) Application number: **89107099.7**

(22) Date of filing: **20.04.89**

## (54) 4-Quinoline carboxylic acid derivatives useful as immunosuppressive agents.

(30) Priority: **26.04.88 US 186243**

(43) Date of publication of application:
**02.11.89 Bulletin 89/44**

(45) Publication of the grant of the patent:
**31.03.93 Bulletin 93/13**

(84) Designated Contracting States:
**AT BE CH DE ES FR GB GR IT LI LU NL SE**

(56) References cited:
**GB-A- 1 334 705**
**US-A- 3 574 840**
**US-A- 4 680 299**

(73) Proprietor: **THE DU PONT MERCK PHARMACEUTICAL COMPANY**
**Barley Mill Plaza, Building 25**
**Wilmington, Delaware 19880-0025(US)**

(72) Inventor: **Ackerman, Neil Richard**
**22 Foxhill Lane**
**Greenville, DE 19807(US)**
Inventor: **Jaffee, Bruce Donald**
**3206 Heathwood Road**
**Wilmington, DE 19810(US)**
Inventor: **Loveless, Scott Edward**
**119 Country Club Drive**
**Newark, DE 19711(US)**
Inventor: **Neubauer, Russell Howard**
**1184 Pynchon Hall Road**
**West Chester, PA 19382(US)**

(74) Representative: **von Kreisler, Alek, Dipl.-Chem. et al**
**Deichmannhaus am Hauptbahnhof**
**W-5000 Köln 1 (DE)**

EP 0 339 485 B1

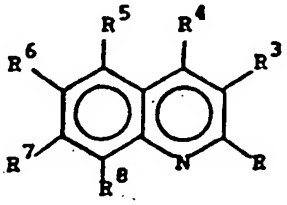
## Description

This invention relates to the use of 4-quinoline carboxylic acids and derivatives thereof for the manufacture of medicaments for the treatment of immunological and inflammatory diseases.

U.S. Patent 4,680,299, granted July 14, 1987, to Hesson describes phenylquinoline carboxylic acids and their derivatives as tumor inhibiting agents.

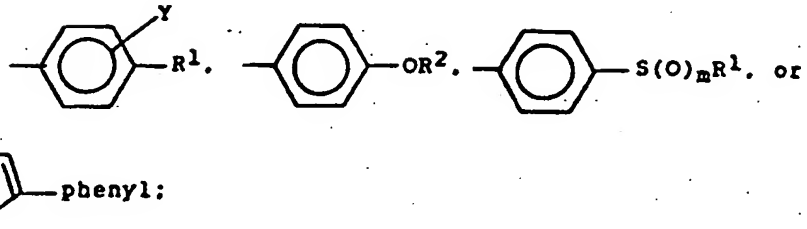
It has now been found that the compounds described in U.S. 4,680,299 are useful as immunomodulatory and antiinflammatory agents.

The present invention relates to the use of a compound having the formula:



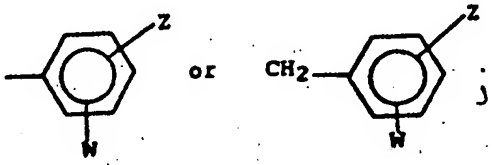
(I)

wherein R is

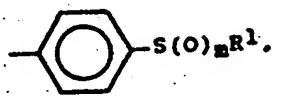




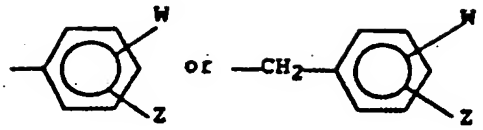
$R^1$ is $CH_3CH_2(CH_3)CH$, alkyl of 5-12 carbon atoms, cyclohexyl,



when R is



| | | |
|---|---|---|
| $R^1$ | | can be in addition alkyl of 3-4 carbon atoms; |
| $R^2$ | | is |

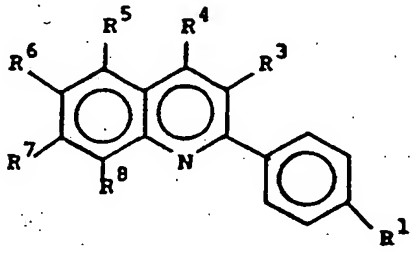


| | |
|---|---|
| $R^3$ | is H, alkoxy of 1-3 carbon atoms, or alkyl of 1-2 carbon atoms; |
| $R^4$ | is $CO_2H$ or $CO_2R^{11}$; |
| $R^5$, $R^6$, $R^7$ and $R^8$ | are independently H, F, Cl, Br, I, $CH_3$, $CF_3$, $SCH_3$ or $CH_2CH_3$, at least two of $R^5$, $R^6$, $R^7$ and $R^8$ being H; |
| $R^9$ and $R^{9A}$ | are independently H or alkyl of 1 to 3 carbon atoms; |
| $R^{11}$ | is $(CH_2)_{2-4}NR^9R^{9A}$; |
| W, Y and Z | are independently H, F, Cl, Br, alkyl of 1-5 carbon atoms, $NO_2$, OH, $CF_3$ or $OCH_3$; |
| m | is 0 or 1; or |

a pharmaceutically suitable salt thereof;
with the following provisos:
(1) $R^5$, $R^6$ and $R^7$ cannot all be H;
(2) when $R^4$ is $CO_2CH_2CH_2N(CH_3)_2$, $R^6$ is $CH_2CH_3$, or $R^7$ is Cl, $R^1$ cannot be cyclohexyl;
(3) when $R^1$ is cyclohexyl and $R^3$ is H, $R^6$ must be Cl or F, but $R^6$ and $R^8$ cannot both be Cl; and
(4) when $R^6$ is $CH_3$, then $R^7$ cannot be Cl.
for preparing medicaments for the treatment of rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, myasthenia gravis, organ transplantation rejection, graft versus host disease, or a chronic inflammatory disease in a mammal.

Additionally, this invention relates to said use wherein the compound is combined with a nonsteroidal antiinflammatory drug.

Preferred compounds useful in the method have the formula:



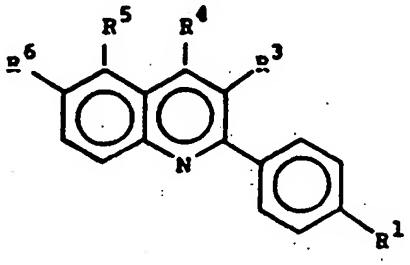
(II)

wherein

| | |
|---|---|
| $R^1$ | is cyclohexyl; phenyl; phenyl substituted with one halogen, alkyl of 1-5 carbon atoms or $CF_3$; phenoxy; or phenoxy substituted with one halogen or alkyl of 1-5 carbon atoms; |
| $R^3$ | is H or alkyl of 1-2 carbon atoms; |
| $R^4$ | is $CO_2H$, a sodium or potassium salt thereof; or $CO^2R^{11}$; |
| $R^5$ and $R^6$ | are independently H, halogen, $CH_3$ or $CF_3$; |
| $R^7$ and $R^8$ | are independently H or halogen; |
| $R^{11}$ | is $(CH_2)_{2-4}NR^9R^{9A}$; and |
| $R^9$ and $R^{9A}$ | are independently alkyl of 1 to 3 carbon atoms, |

or a pharmaceutically suitable salt thereof;
provided that $R^5$, $R^6$ and $R^7$ cannot all be H and that when $R^1$ is cyclohexyl and $R^3$ is H, $R^6$ must be Cl or F, but $R^6$ and $R^8$ cannot both be Cl, and when $R^6$ is $CH_3$, then $R^7$ cannot be Cl.

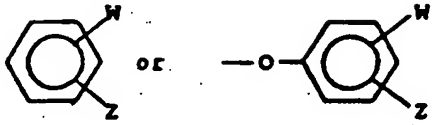
More preferred compounds useful in this invention have the formula:



(III)

wherein

$R^1$ is cyclohexyl,



$R^3$ is H or alkyl of 1-2 carbon atoms;

$R^4$ is $CO_2H$, a sodium or potassium salt thereof, or $CO_2R^{11}$;

$R^5$ and $R^6$ are independently H, halogen or $CF_3$ provided that both $R^5$ and $R^6$ are not hydrogen;

$R^{11}$ is $(CH_2)_{2-4}NR^9R^{9A}$; and

$R^9$ and $R^{9A}$ are independently alkyl of 1 to 3 carbon atoms, and

W and Z are independently H, halogen, alkyl of 1-5 carbon atoms or $CF_3$;

provided that when $R^1$ is phenyl or phenoxy, and $R^5$ is H, then $R^6$ cannot be Br; and that when $R^1$ is cyclohexyl and $R^3$ is H, $R^6$ must be Cl or F.

Specifically preferred compounds useful in this invention are:

(1) 2-(1,1'-biphenyl-4-yl)-5-chloro-3-methyl-4-quinoline carboxylic acid, sodium or potassium salt

(2) 2-(1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinoline carboxylic acid, sodium or potassium salt

(3) 6-fluor-3-methyl-2-(4-phenoxyphenyl)-4-quinoline carboxylic acid, sodium or potassium salt

(4) 2-(4'-bromo-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinoline carboxylic acid, sodium or potassium salt

(5) 2-(2'-fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinoline carboxylic acid, sodium or potassium salt.

The compounds useful in this invention are described in and prepared by methods set forth in U.S. Patent 4,680,299.

The invention can be further understood by the following examples in which parts and percentages are by weight unless otherwise indicated; all temperatures are in degrees centigrade.

Example 1

Part A:

2-(1,1'-Biphenyl-4-yl)-5-chloro-3-methyl-quinoline-4-carboxylic acid

A mixture of 4-chloroisatin (7.28 g, .04 mol), [J. Am. Chem. Soc., 1251 (1956)], 4-phenylpropiophenone (8.8 g, .04 mol), diethylamine (4 ml, .04 mol) and ethanol (200 ml) was stirred for a period of 18 hours at room temperature. The precipitated solids were collected by filtration, washed with ice-cold ethanol and air dried to yield the adduct (9.1 g, 58%) m.p. 209-214° dec.

Part B:

The above described adduct (9.1 g) was added to a mixture of tetrahydrofuran (200 ml), and concentrated HCl (200 ml) and heated at reflux for 24 hr. The reaction mixture was cooled, water (300 ml) was added and most of the tetrahydrofuran removed by evaporation in vacuo. The aqueous residue was cooled and the sticky solids collected by filtration. Trituration in 150 ml of boiling methanol yielded (4.8 g, 55%) m.p. 295-297° dec.

$C_{23}H_{16}ClNO_2$ HRMS: 373.0869 Calcd, measured m/e 373.0814.

$^1H$ NMR (DMSO-$d_6$):$\delta$ 8.5(m,1H), 7.7-7.85(m,7H), 7.35-7.55(m,4H), 2.45(s,3H).

Part C:

Sodium 2-(1,1′-Biphenyl-4-yl)-5-chloro-3-methyl-quinoline-4-carboxylate

To a suspension of the above acid (3.7 g, .01 mol) in ethanol 100 ml, sodium hydroxide (1N, 10 ml, .01 mol) was added, and gently warmed. The clear solution was then filtered and evaporated to dryness to yield (4.0 g) m.p. 320-330° dec.

Example 2

Part A:

2-(2-Fluoro-1,1′-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinoline carboxylic acid

5-Fluoroisatin (72.6 g, 0.44 mol) and 4-(2-fluorophenyl)propiophenone (100 g, 0.44 mole) were suspended in 720 ml of ethanol and stirred mechanically as a solution of KOH (147.8 g, 2.64 mole) in 300 ml of water was added dropwise over 15 minutes. The reaction mixture was heated at reflux for 12 hours, cooled and the ethanol evaporated under reduced pressure. The resulting solid was dissolved in water and washed with ethyl ether. The aqueous layer was cooled to 5° and acidified with glacial acetic acid. The resulting precipitate was filtered, washed 2 times with 300 ml of ethyl ether and dried. Recrystallization from dimethylformamide and water gave 84 g of a white 2-(2′-Fluoro-1,1′-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinoline carboxylic acid, m.p. 315°-317°.

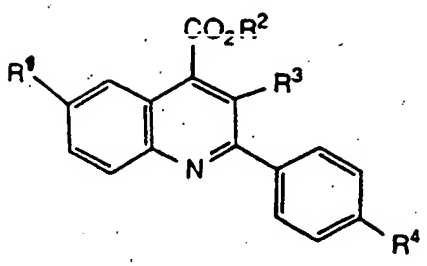
Part B:

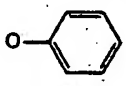
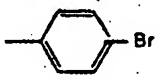
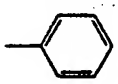
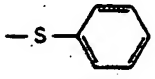
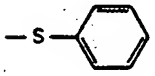
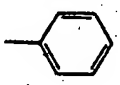
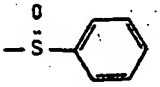
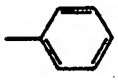
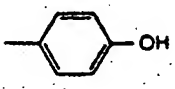
Sodium 2-(2′-Fluoro-1,1′-biphenyl-4-yl)-6-fluoro-3-methylquinoline-4-carboxylate

The compound of Part A (37.5 g, 0.10 mole) was suspended in 1,000 ml of ethanol and treated with 1N NaOH (100 ml, 0.10 mole). The mixture was warmed and stirred until clear; the ethanol and water were evaporated at reduced pressure to give 39.6 g of the white solid sodium 2-(2′-fluoro-1,1′-biphenyl-4-yl)6-fluoro-3-methylquinoline-4-carboxylate, m.p. >360°.

Following the procedures of Examples 1 and 2 or the synthesis procedures described in U.S. 4,680,299, the compounds set forth in Table 1 were prepared.

Table 1




| Ex. No. | $R^1$ | $R^2$ | $R^3$ | R4 | m.p.(°) |
|---|---|---|---|---|---|
| 3 | F | Na | $CH_3$ |  | >350 |
| 4 | F | Na | $CH_3$ |  | >350 |
| 5 | $CH_3$ | Na | $CH_3$ |  | >350 |
| 6 | F | Na | $CH_3$ | $-S-CH(CH_3)_2$ | 339-343 |
| 7 | Cl | Na | $CH_3$ |  | 319-324 |
| 8 | Cl | K | $CH_3$ |  | 310-325 |
| 9 | F | Na | H |  | >360 |
| 10 | F | Na | $CH_3$ |  | 251-260 |
| 11 | F | Na | $OCH_3$ |  | 345-349 |
| 12 | Cl | Na | $CH_3$ |  | >360 |

Utility

Results of the biological tests described below establish that the compounds useful in this invention have the ability to suppress/inhibit: the contact sensitivity response to 2,4-dinitrofluorobenzene (DNFB) in mice, the human mixed lymphocyte reactions, and adjuvant-induced arthritis in rats.

Contact sensitivity to DNFB has been extensively studied and characterized in the mouse to determine the regulatory mechanisms involved in cell mediated immune responses (Claman, et al., Immunol Rev

50:105, 1980). This is an antigen-specific T-cell mediated inflammatory response that represents delayed-type hypersensitivity reactions seen in both humans and other mammals. The primary use of the human mixed lymphocyte reaction is for the determination of transplantation compatibility between the donor (graft) and the recipient (Park and Good, p. 71. In Yunis, et al., Tissue typing and organ transplantation. 1973 Academic Press Inc., N.Y.).

Rat adjuvant-induced arthritis represents a systemic inflammatory disease with bone and cartilage changes similar to that observed in rheumatoid arthritis, but in an accelerated time span (Pearson, Arth Rheum 7:80, 1964).

Most clinically effective drugs exhibit activity in these biological tests similar to that observed with the compounds useful in this invention (Fenichel and Chirigos, ed, Immune modulation agents and their mechanisms, 1984 Dekker, Inc, N.Y., and Billingham, 21:389, 1983).

Contact Sensitivity Response to DNFB in Mice

Balb/c female mice (≈ 20g, Charles River) were sensitized on the shaved abdomen with 25 µl of 0.5% 2,4-dinitrofluorobenzene (DNFB, Eastman Kodak Co.) in a vehicle of 4:1 acetone:olive oil on days 0 and 1. Mice were ear challenged with 20 µl of 0.2% DNFB in a vehicle of 4:1 acteone:olive oil on day 5. A constant area of the ears was measured immediately before challenge and 24 hours later with an engineer's micrometer. Ear swelling was expressed as the difference in ear thickness before and after challenge in units of $10^{-4}$ inches ± SEM. Percent suppression was calculated as:

$$\% \text{ Suppression} = 1 - \frac{\text{compound treated-negative control}}{\text{positive control-negative control}} \times 100$$

Compounds were administered orally from days - 2 through day 6 and were prepared in 0.25% Methocel® (Dow Chemical Co.). Control animals received only vehicle (0.25% Methocel®). Negative controls were not sensitized on days 0 and 1 but were ear challenged on day 5. Ten mice were used per group. Results with compounds of invention and drugs used clinically are shown in Tables 2 and 3.

Table 2

| Treatment | Dose (mg/kg) | Ear Swelling[a] (units ± SEM) | % Suppression | $ED_{50}$ |
|---|---|---|---|---|
| Negative | Vehicle | 0.74±0.52 | - | - |
| Positive | Vehicle | 74.11±3.78 | 0 | - |
| Dexamethasone | 0.2 | 52.95±3.39 | 28.84 | 1.50 |
| | 1.0 | 41.60±2.46 | 44.31 | |
| | 5.0 | 23.79±2.71 | 68.58 | |
| | 10.0 | 15.50±2.10 | 79.88 | |
| Cyclosporin A | 2.0 | 56.15±3.74 | 24.48 | 70.00 |
| | 10.0 | 66.58±3.75 | 10.27 | |
| | 50.0 | 47.90±3.76 | 35.72 | |
| | 100.0 | 7.80±2.04 | 90.37 | |
| Methotrexate | 0.4 | 71.30±2.96 | 3.83 | 9.00 |
| | 2.0 | 60.80±1.99 | 18.14 | |
| | 10.0 | 36.10±3.23 | 51.80 | |
| | 20.0 | 27.45±4.99 | 63.59 | |
| Example 1 | 0.4 | 66.05±4.32 | 10.99 | 3.50 |
| | 2.0 | 56.94±4.80 | 23.40 | |
| | 10.0 | 6.10±0.75 | 92.69 | |
| | 20.0 | 5.20±1.17 | 93.92 | |
| Example 2 | 0.4 | 51.95±2.33 | 30.20 | 0.95 |
| | 2.0 | 25.61±3.39 | 66.10 | |
| | 10.0 | 6.40±1.09 | 92.28 | |
| | 20.0 | 4.75±1.20 | 94.53 | |

[a] Increase in ear thickness from day 5 to day 6, unit = $10^{-4}$ inches

TABLE 3

| Treatment | Dose (mg/kg) | Ear Swelling[a] (units ± SEM) | % Suppression |
|---|---|---|---|
| Negative | Vehicle | 2.60±0.73 | - |
| Positive | Vehicle | 73.11±3.69 | 0 |
| Dexamethasone | 1.0 | 42.20±2.61 | 43.83 |
| Cyclosporin A | 20.0 | 74.30±2.86 | -1.69 |
| Methotrexate | 20.0 | 16.94±2.10 | 79.66 |
| Example 3 | 20.0 | 14.25±1.49 | 83.48 |
| Example 4 | 20.0 | 11.80±1.03 | 86.95 |
| Example 5 | 20.0 | 35.47±2.31 | 53.37 |
| Example 6 | 20.0 | 58.20±4.63 | 21.14 |
| Example 7 | 20.0 | 62.95±3.40 | 14.40 |
| Example 8 | 20.0 | 63.25±3.58 | 13.98 |
| Example 9 | 20.0 | 42.60±2.68 | 43.27 |
| Example 10 | 20.0 | 57.28±2.36 | 22.45 |
| Example 11 | 20.0 | 20.85±2.53 | 74.12 |
| Example 12 | 20.0 | 54.58±3.21 | 26.28 |

[a] increase in ear thickness from day 5 to day 6, unit = $10^{-4}$

Human Mixed Lymphocyte Reaction

Blood was obtained by venipunture from two nonrelated human donors. Peripheral blood mono-nuclear cells (PBMC) were isolated from these samples by using the Leuco Prep procedure (Becton-Dickinson). PBMC were washed twice in phosphate buffered saline (without calcium and magnesium) and the separate cell isolations were adjusted to the appropriate concentrations in media (RPMI 1640) supplemented with 20% human AB serum and 50 µl/ml gentamicin. Cells from donor A ($2 \times 10^5$) were incubated with cells from donor B ($2 \times 10^5$) in 96 well round bottom microliter plate at 37° C, 5% $CO_2$ for 6 days. Eighteen hours prior to harvesting cells from the plates, all wells were pulsed with 1 µCi of $^3$H-thymidine. Cells from the plates were harvested on day 6 and $^3$H-thymidine incorporation was determined using a scintillation counter. Test results are shown in Table 4.

TABLE 4

| Compound | $IC_{50}$ (M) |
|---|---|
| Indomethacin | $> 10^{-6}$ |
| Cyclosporin A | $1.6 \times 10^{-8}$ |
| Methotrexate | $2.5 \times 10^{-9}$ |
| Example 1 | $9.6 \times 10^{-9}$ |
| Example 2 | $2.5 \times 10^{-8}$ |

Adjuvant-Induced Arthritis

Male Lewis rats (Charles River) weighing 160-210 grams were injected subcutaneously with 0.1 ml of Freund's Complete Adjuvant containing 5 mg of M. butyricum/ml of paraffin oil (Difco Laboratories) into the plantar region of the right hind paw. Paraffin oil was injected for non-arthritic controls. Ten rats were used per group Compounds were prepared in 0.25% Methocel® (Dow Chemical Co) with one drop of Tween® 80 per 10 ml of Methocel®. Animals were dosed every day beginning on the day of paw injection until day 18. The weight of each animal was recorded every other day beginning on the day of the paw injections. On day 18 the animals were weighed, and the non-injected hind paw volume was measured using a Ugo Basile Volume Differential Plethysmometer. The results are shown in Table 5.

TABLE 5

| Group (AA) | Compound (mg/kg) | Weight Gain (g) | Non-Injected Hind-Paw Volume (ml) | % Suppression |
|---|---|---|---|---|
| A - | Vehicle | 85.6±4.8 | 1.12±0.01 | - |
| B + | Vehicle | -20.3±2.9 | 1.88±0.05 | - |
| C + | Example 1 (10.00) | -14.0±4.2 | 1.87±0.08 | 1.4 |
| D + | Example 1 (17.5) | 2.8±5.3 | 1.72±0.08 | 20.8 |
| E + | Example 1 (25.0) | 20.6±6.3 | 1.34±0.10 | 70.6 |
| F + | Example 2 (2.0) | - 1.5±3.6 | 1.62±0.05 | 34.5 |
| G + | Example 2 (10.0) | 65.6±5.2 | 1.15±0.02 | 96.2 |
| H + | Example 2 * (25.0) | | | |
| Example 1: $ED_{50}$ = 21 mg/kg<br>Example 2: $ED_{50}$ < 10 mg/kg | | | | |

*Toxic by day 7

In summary, test results show that the compounds useful in this invention have both immunomodulating and anti-inflammatory effectiveness. Based on these data, the compounds useful in this invention should be efficacious in treating autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematous, multiple sclerosis, and myastenia gravis; all of which involve T lymphocyte mediated components similar to those known in the contact sensitivity model. Activities in the human mixed lymphocyte reaction indicate that the compounds of invention should be effective in preventing transplantation rejection and graft vs. host

disease. These compounds were also effective in the adjuvant-induced arthritis model and should therefore be useful antiinflammatory agents for the treatment of chronic inflammatory diseases such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease.

## DOSAGE FORMS

The immunosuppressive compounds (active ingredients) of this invention can be administered to inhibit tumors by any means that produces contact of the active ingredient with the agent's site of action in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals; either as individual therapeutic active ingredients or in a combination of therapeutic active ingredients. They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will be an immunosuppressive amount of active ingredient and will, of course, vary depending upon known factors such as the pharmacodynamic characteristics of the particular active ingredient, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms; kind of concurrent treatment, frequency of treatment, and the effect desired. Usually a daily dosage of active ingredient can be about 0.1 to 400 milligrams per kilogram of body weight. Ordinarily 1 to 100, and preferably 10 to 50 milligrams per kilogram per day is effective to obtain desired results.

Dosage forms (compositions) suitable for internal administration contain from about 10-500 milligrams to about 500 milligrams of active ingredient per unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions, it can also be administered parenterally, in sterile liquid dosage forms.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions, it can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, sucrose, mannitol, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration contain preferably a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid either alone or combined are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, A. Osol, a standard reference text in this field.

## CAPSULES

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 175 milligrams of lactose, 24 milligrams of talc, and 6 milligrams magnesium stearate.

A mixture of active ingredient in soybean oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

TABLETS

A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of cornstarch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

INJECTABLE

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized.

SUSPENSION

AN aqueous suspension is prepared for oral administration so that each 5 milliliters contain 100 milligrams of finely divided active ingredient, 200 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin.

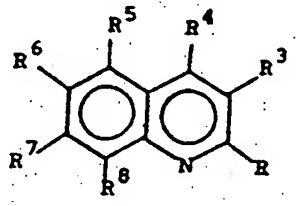
The same dosage forms can generally be used when the compounds of this invention are administered stepwise in conjunction with another therapeutic agent. When the drugs are administered in physical combination, the dosage form and administration route should be selected for compatibility with both drugs. Suitable dosages, dosage forms and administration routes are illustrated in Table 6.

Table 6

| Examples of NSAID's that can be combined with the 4-quinolinecarboxylic acids used in this invention | | |
|---|---|---|
| Drug | Dose (mg) | Formulation Route |
| Indomethacin | 25 (2/3 times daily) | Tablet Oral |
| Meclofenamate | 50-100 (2/3 times daily) | Tablet Oral |
| Ibuprofen | 300-400 (3/4 times daily) | Tablet Oral |
| Piroxicam | 10-20 (1/2 times daily) | Tablet Oral |
| Sulindac | 150-200 (2 times daily) | Tablet Oral |
| Azapropazone | 200-500 (3/4 times daily) | Tablet Oral |

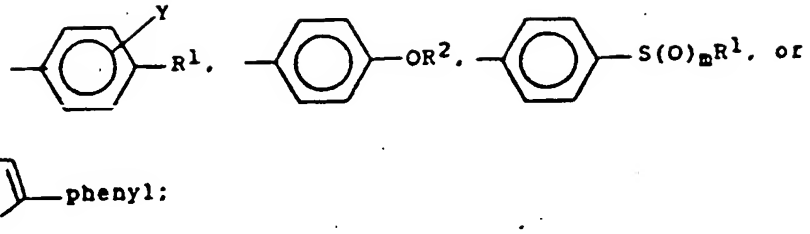
**Claims**

1. Use of compounds having the formula:



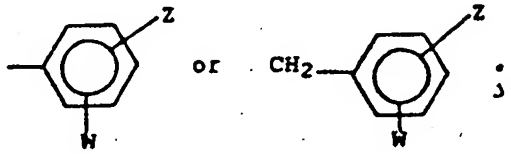
(I)

wherein R is

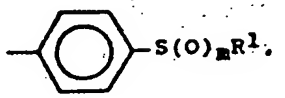




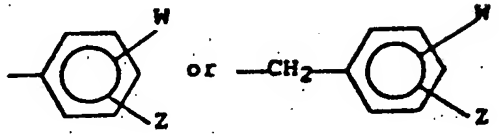
$R^1$ is $CH_3CH_2(CH_3)CH$, alkyl of 5-12 carbon atoms, cyclohexyl,



when R is



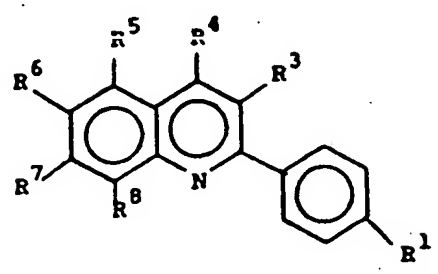
| | | |
|---|---|---|
| | $R^1$ | can be in addition alkyl of 3-4 carbon atoms; |
| | $R^2$ | is |



| | | |
|---|---|---|
| | $R^3$ | is H, alkoxy of 1-3 carbon atoms, or alkyl of 1-2 carbon atoms; |
| | $R^4$ | is $CO_2H$ or $CO_2R^{11}$; |
| | $R^5$, $R^6$, $R^7$ and $R^8$ | are independently H, F, Cl, Br, I, $CH_3$, $CF_3$, $SCH_3$ or $CH_2CH_3$, at least two of $R^5$, $R^6$, $R^7$ and $R^8$ being H; |
| | $R^9$ and $R^{9A}$ | are independently H or alkyl of 1 to 3 carbon atoms; |
| | $R^{11}$ | is $(CH_2)_{2-4}NR^9R^{9A}$; |
| | W, Y and Z | are independently H, F, Cl, Br, alkyl of 1-5 carbon atoms, $NO_2$, OH, $CF_3$ or $OCH_3$; |
| | m | is 0 or 1; or |

a pharmaceutically suitable salt thereof;
with the following pravisos:
(1) $R^5$, $R^6$ and $R^7$ cannot all be H;
(2) when $R^4$ is $CO_2CH_2CH_2N(CH_3)_2$, $R^6$ is $CH_2CH_3$, or $R^7$ is Cl, $R^1$ cannot be cyclohexyl;
(3) when $R^1$ is cyclohexyl and $R^3$ is H, $R^6$ must be Cl or F, but $R^6$ and $R^8$ cannot both be Cl; and
(4) when $R^5$ is $CH_3$, then $R^7$ cannot be Cl
for preparing medicaments for the treatment of rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, myasthenia gravis, organ transplantation rejection, graft versus host disease, or a chronic inflammatory disease in a mammal.

2. The use of Claim 1 wherein the compound has the formula:



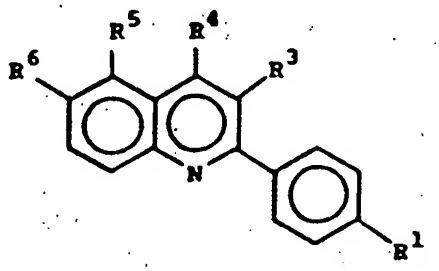
(II)

wherein

| | |
|---|---|
| $R^1$ | is cyclohexyl; phenyl; phenyl substituted with one halogen, alkyl of 1-5 carbon atoms or $CF_3$; phenoxy; or phenoxy substituted with one halogen or alkyl of 1-5 carbon atoms; |
| $R^3$ | is H or alkyl 1-2 carbon atoms; |
| $R^4$ | is $CO_2H$, a sodium or potassium salt thereof; or $CO^2R^{11}$; |
| $R^5$ and $R^6$ | are independently H, halogen, $CH_3$ or $CF_3$; |
| $R^7$ and $R^8$ | are independently H or halogen; |
| $R^{11}$ | is $(CH_2)_{2-4}NR^9R^{9A}$; and |
| $R^9$ and $R^{9A}$ | are independently alkyl of 1 to 3 carbon atoms, |

or a pharmaceutically suitable salt thereof;
provided that $R^5$, $R^6$ and $R^7$ cannot all be H and that when $R^1$ is cyclohexyl and $R^3$ is H, $R^6$ must be Cl or F, but $R^6$ and $R^8$ cannot both be Cl, and when $R^6$ is $CH_3$, then $R^7$ cannot be Cl.

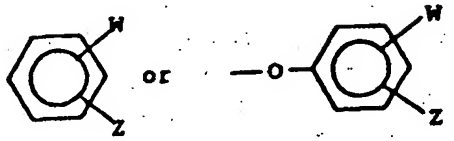
3. The use of Claim 1 wherein the compound has the formula:



(III)

wherein

| | |
|---|---|
| $R^1$ | is cyclohexyl, |



| | |
|---|---|
| $R^3$ | is H or alkyl of 1-2 carbon atoms; |
| $R^4$ | is $CO_2H$, a sodium or potassium salt thereof, or $CO_2R^{11}$; |
| $R^5$ and $R^6$ | are independently H, halogen or $CF_3$ provided that both $R^5$ and $R^6$ are not hydrogen; |
| $R^{11}$ | is $(CH_2)_{2-4}NR^9R^{9A}$; and |

$R^9$ and $R^{9A}$ are independently alkyl of 1 to 3 carbon atoms, and
W and Z are independently H, halogen, alkyl of 1-5 carbon atoms or $CF_3$;
provided that when $R^1$ is phenyl or phenoxy, and $R^5$ is H, then $R^6$ cannot be Br; and that when $R^1$ is cyclohexyl and $R^3$ is H, $R^6$ must be Cl or F.

4. The use of Claim 1 wherein the compound is 2-(1,1'-biphenyl-4-yl)-5-chloro-3-methyl-4-quinoline carboxylic acid, sodium or potassium salt.

5. The use of Claim 1 wherein the compound is 2-(1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinoline carboxylic acid, sodium or potassium salt.

6. The use of Claim 1 wherein the compound is 6-fluoro-3-methyl-2-(4-phenoxyphenyl)-4-quinoline carboxylic acid, sodium or potassium salt.

7. The use of Claim 1 wherein the compound is 2-(4'-bromo-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinoline carboxylic acid, sodium or potassium salt.

8. The use of Claim 1 wherein the compound is 2-(2'-fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinoline carboxylic acid, sodium or potassium salt.

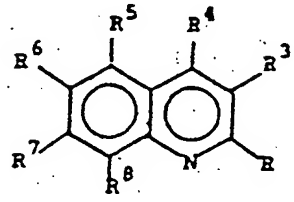
9. The use of Claim 1 wherein the compound is combined with a nonsteroidal antiinflammatory drug.

10. The use of Claim 4 wherein the compound is combined with a nonsteroidal antiinflammatory drug.

11. The use of Claim 8 wherein the compound is combined with a nonsteroidal antiinflammatory drug.

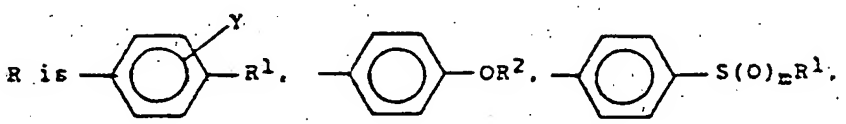
**Patentansprüche**

1. Verwendung von Verbindungen der Formel:

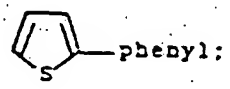


(I)

worin R

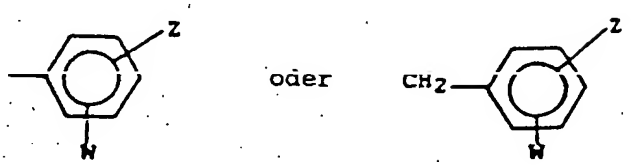



oder

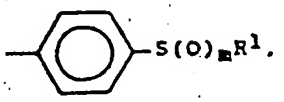



ist;

$R^1$ $CH_3CH_2(CH_3)CH$, Alkyl mit 5 - 12 Kohlenstoffatomen, Cyclohexyl,

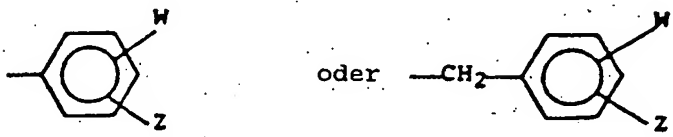



ist;
wenn R




ist,
kann $R^1$ zusätzlich ein Alkyl mit 3 - 4 Kohlenstoffatomen sein;

$R^2$




ist;

| | |
|---|---|
| $R^3$ | H, Alkoxy mit 1 - 3 Kohlenstoffatomen, oder Alkyl mit 1 - 2 Kohlenstoffatomen ist; |
| $R^4$ | $CO_2H$ oder $CO_2R^{11}$ ist; |
| $R^5$, $R^6$, $R^7$ und $R^8$ | unabhängig von einander H, F, Cl, Br, J, $CH_3$, $CF_3$, $SCH_3$ oder $CH_2CH_3$ sind, wobei wenigstens zwei der $R^5$, $R^6$, $R^7$ und $R^8$ H sind; |
| $R^9$ und $R^{9A}$ | unabhängig von einander H oder Alkyl mit 1 - 3 Kohlenstoffatomen sind; |
| $R^{11}$ | $(CH_2)_{2-4}NR^9R^{9A}$ ist; |
| W, Y und Z | unabhängig von einander H, F, Cl, Br, Alkyl mit 1 - 5 Kohlenstoffatomen, $NO_2$, OH, $CF_3$ oder $OCH_3$ sind; |
| m | 0 oder 1 ist; oder |

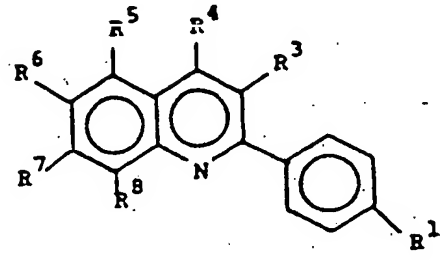
ein pharmazeutisch annehmbares Salz davon;
mit folgenden Maßgaben:

(1) $R^5$, $R^6$ und $R^7$ können nicht alle H sein;
(2) wenn $R^4$ $CO_2CH_2CH_2N(CH_3)_2$ ist, ist $R_6$ $CH_2CH_3$, oder $R^7$ Cl ist, kann $R^1$ nicht Cyclohexyl sein;
(3) wenn $R^1$ Cyclohexyl und $R^3$ H ist, muß $R^6$ Cl oder F sein, aber $R^6$ und $R^8$ können nicht beide Cl sein; und
(4) wenn $R^6$ $CH_3$ ist, kann $R^7$ nicht Cl sein,

zur Herstellung von Medikamenten für die Behandlung von rheumatischer Arthritis, systemischem Lupus erythematodes, multipler Sklerose, Myasthenia gravis, Abstoßung von Organtransplantaten, Transplantat-gegen-Wirt Krankheit oder einer chronischen Entzündung in einem Säuger.

2. Verwendung nach Anspruch 1, worin die Verbindung die Formel hat:

(II)



worin

$R^1$ Cyclohexyl; Phenyl; mit einem Halogen, Alkyl mit 1 - 5 Kohlenstoffatomen oder $CF_3$ substituierten Phenyl; Phenoxy oder mit einem Halogen oder Alkyl mit 1 - 5 Kohlenstoffatomen substituierten Phenoxy ist;

$R^3$ H oder Alkyl mit 1 - 2 Kohlenstoffatomen ist;

$R^4$ $CO_2H$, ein Natrium- oder Kaliumsalz davon; oder $CO_2R^{11}$ ist;

$R^5$ und $R^6$ unabhängig von einander H, Halogen, $CH_3$ oder $CF_3$ sind;

$R^7$ und $R^8$ unabhängig von einander H oder Halogen sind;

$R^{11}$ $(CH_2)_{2-4}NR^9R^{9A}$ ist; und

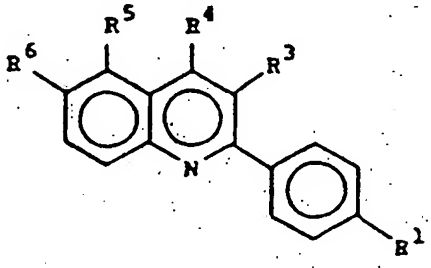
$R^9$ und $R^{9A}$ unabhängig von einander Alkyl mit 1 - 3 Kohlenstoffatomen sind

oder einem pharmazeutisch annehmbaren Salz davon;

mit der Maßgabe, daß $R^5$, $R^6$ und $R^7$ nicht alle H sein können und daß, wenn $R^1$ Cyclohexyl und $R^3$ H ist, $R^6$ Cl oder F sein muß, aber $R^6$ und $R^8$ nicht beide Cl sein können, und wenn $R^6$ $CH_3$ ist, $R^7$ nicht Cl sein kann.

3. Verwendung nach Anspruch 1, worin die Verbindung die Formel hat:

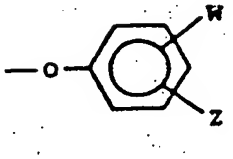
(III)



worin

$R^1$ Cyclohexyl,

oder



ist;

$R^3$ H oder Alkyl mit 1 - 2 Kohlenstoffatomen ist;

| | |
|---|---|
| $R^4$ | $CO_2H$, ein Natrium- oder Kaliumsalz davon oder $CO_2R^{11}$ ist; |
| $R^5$ und $R^6$ | unabhängig von einander H, Halogen oder $CF_3$ sind, mit der Maßgabe, daß nicht beide $R^5$ und $R^6$ Wasserstoff sind; |
| $R^{11}$ | $(CH_2)_{2-4}NR^9R^{9A}$ ist; und |
| $R^9$ und $R^{9A}$ | unabhängig von einander Alkyl mit 1 - 3 Kohlenstoffatomen sind, und |
| W und Z | unabhängig von einander H, Halogen, Alkyl mit 1 - 5 Kohlenstoffatomen oder $CF_3$ sind; |

mit der Maßgabe, daß, wenn $R_1$ Phenyl oder Phenoxy ist und $R_5$ H ist, dann $R^6$ nicht Br sein kann; und daß, wenn $R^1$ Cyclohexyl und $R_3$ H sind, $R^6$ Cl oder F sein muß.

4. Verwendung nach Anspruch 1, worin die Verbindung 2-(1,1'-Biphenyl-4yl)-5-chlor-3-methyl-4-chinolincarbonsäure, Natrium- oder Kaliumsalz ist.

5. Verwendung nach Anspruch 1, worin die Verbindung 2-(1,1'-Biphenyl-4yl)-6-fluor-3-methyl-4-chinolincarbonsäure, Natrium- oder Kaliumsalz ist.

6. Verwendung nach Anspruch 1, worin die Verbindung 6-Fluor-3-methyl-2-(4-phenoxyphenyl)-4-chinolincarbonsäure, Natrium- oder Kaliumsalz ist.

7. Verwendung nach Anspruch 1, worin die Verbindung 2-(4'-Brom-1,1'-biphenyl-4yl)-6-fluor-3-methyl-4-chinolincarbonsäure, Natrium- oder Kaliumsalz ist.

8. Verwendung nach Anspruch 1, worin die Verbindung 2-(2'-Fluor-1,1'-biphenyl-4yl)-6-fluor-3-methyl-4-chinolincarbonsäure, Natrium- oder Kaliumsalz ist.

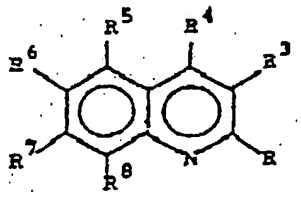
9. Verwendung nach Anspruch 1, worin die Verbindung mit einem nicht-steroiden, entzündungshemmenden Medikament kombiniert ist.

10. Verwendung nach Anspruch 4, worin die Verbindung mit einem nicht-steroiden, entzündungshemmenden Medikament kombiniert ist.

11. Verwendung nach Anspruch 8, worin die Verbindung mit einem nicht-steroiden, entzündungshemmenden Medikament kombiniert ist.

**Revendications**

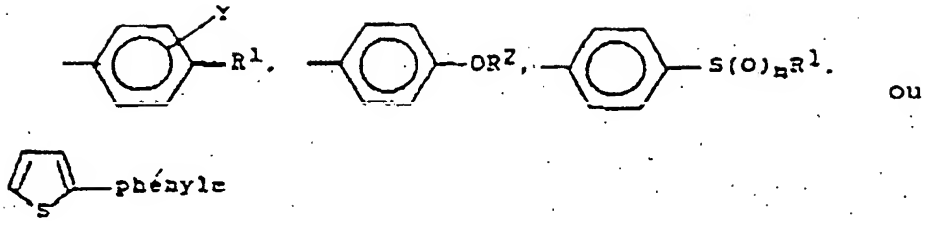
1. Utilisation de composés ayant la formule:



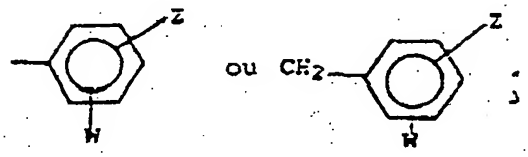
(I)

dans laquelle:

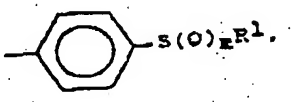
R est




$R^1$ est un radical $CH_3CH_2(CH_3)CH$, alkyle ayant de 5 à 12 atomes de carbone, cyclohexyle,

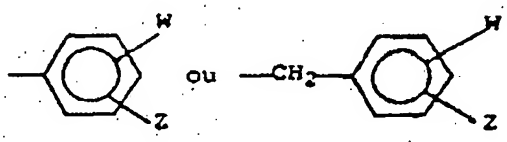



quand R est




$R_1$ peut être en outre un radical alkyle ayant 3-4 atomes de carbone;

$R^2$ est




$R^3$ est H ou un radical alcoxy ayant 1-3 atomes de carbone ou alkyle ayant 1-2 atomes de carbone;

$R^4$ est $CO_2H$ ou $CO_2R^{11}$;

$R^5$, $R^6$, $R^7$ et $R^8$, indépendamment les uns des autres, sont chacun H, F, Cl, Br, I, $CH_3$, $CF_3$, $SCH_3$ ou $CH_2CH_3$, au moins deux des radicaux $R^5$, $R^6$, $R^7$ et $R^8$ étant H;

$R^9$ et $R^{9A}$, indépendamment l'un de l'autre, sont chacun H ou un radical alkyle ayant de 1 à 3 atomes de carbone;

$R^{11}$ est $(CH_2)_{2-4}NR^9R^{9A}$;

W, Y et Z, indépendamment les uns des autres, sont chacun H, F, Cl, Br ou un radical alkyle ayant de 1 à 5 atomes de carbone, $NO_2$, OH, $CF_3$ ou $OCH_3$;

m vaut 0 ou 1;

ou l'un de leurs sels pharmaceutiquement acceptables; étant entendu que:

(1) $R^5$, $R^6$ et $R^7$ ne peuvent tous être H;

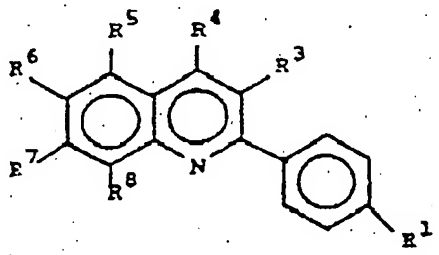
(2) quand $R^4$ est $CO_2CH_2CH_2N(CH_3)_2$, $R^6$ est $CH_2CH_3$, ou encore $R^7$ est Cl, $R^1$ ne peut être un radical cyclohexyle ;

(3) quand $R^1$ est un radical cyclohexyle et $R^3$ est H, $R^6$ doit être Cl ou F, mais $R^6$ et $R^8$ ne peuvent être tous les deux Cl; et

(4) quand $R^6$ est $CH_3$, alors $R^7$ ne peut être Cl,

pour préparer des medicaments destinés aux traitements de l'arthrite rhumatoïde, du lupus érythémateux aigu disséminé, de la sclérose en plaques, de la myasthénie grave, du rejet des transplantations d'organes, de la réaction du greffon contre hôte ou d'une maladie inflammatoire chronique chez un mammifère.

2. L'utilisation selon la revendication 1, dans laquelle le composé a la formule:

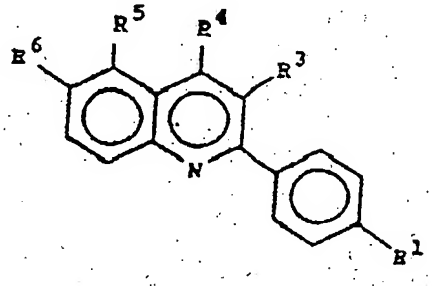


dans laquelle:

| | |
|---|---|
| $R^1$ | est un radical cyclohexyle; phényle; phényle substitué par un halogène, un radical alkyle ayant de 1 à 5 atomes de carbone ou $CF_3$; phénoxy; ou phénoxy substitué par un halogène ou un radical alkyle ayant de 1 à 5 atomes de carbone; |
| $R^3$ | est H ou un radical alkyle ayant 1-2 atomes de carbone; |
| $R^4$ | est $CO_2H$, un de ses sels de sodium ou de potassium; ou $CO_2R^{11}$; |
| $R^5$ et $R^6$, | indépendamment l'un de l'autre, sont chacun H ou un halogène, $CH_3$ ou $CF_3$; |
| $R^7$ et $R^8$, | indépendamment l'un de l'autre, sont chacun H ou un halogène; |
| $R^{11}$ | est $(CH_2)_{2-4}NR^9R^{9A}$; et |
| $R^9$ et $R^{9A}$, | indépendamment l'un de l'autre, sont chacun un radical alkyle ayant de 1 à 3 atomes de carbone, |

ou un de leurs sels pharmaceutiquement acceptable; du moment que $R^5$, $R^6$ et $R^7$ ne peuvent tous être H et que, quand $R^1$ est un radical cyclohexyle et $R^3$ est H, $R^6$ doit être Cl ou F, mais $R^6$ et $R^8$ ne peuvent être simultanément Cl et, quand $R^6$ est $CH_3$, alors $R^7$ ne peut être Cl.

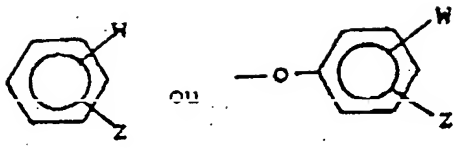
3. L'utilisation selon la revendication 1, dans laquelle le composé a la formule:



(III)

dans laquelle:

| | |
|---|---|
| $R^1$ | est un radical cyclohexyle, |



| | | |
|---|---|---|
| | $R^3$ | est H ou un radical alkyle ayant 1-2 atomes de carbone; |
| | $R^4$ | est $CO_2H$, un de ses sels de sodium ou de potassium, ou encore $CO_2R^{11}$; |
| | $R^5$ et $R^6$, | indépendamment l'un de l'autre, sont chacun H, un halogène ou le radical $CF_3$ du moment que les deux radicaux $R^5$ et $R^6$ ne sont pas simultanément des hydrogènes ; |
| | $R^{11}$ | est $(CH_2)_{2-4}NR^9R^{9A}$ ; et |
| | $R^9$ et $R^{9A}$, | indépendamment l'un de l'autre sont chacun un radical alkyle ayant de 1 à 3 atomes de carbone, et |
| | W et Z, | indépendamment l'un de l'autre, sont chacun H, un halogène ou un radical alkyle ayant de 1 à 5 atomes de carbone ou $CF_3$ ; |

du moment que, quand $R^1$ est le radical phényle ou phénoxy et $R^5$ est H, alors $R^6$ ne peut être Br ; et que, quand $R^1$ est le radical cyclohexyle, et $R^3$ est H, $R^6$ doit être Cl ou F.

4. L'utilisation selon la revendication 1, dans laquelle le composé est le sel de sodium ou de potassium de l'acide 2-(1,1'-biphényl)-4-yl)-5-chloro-3-méthyl-4-quinoléinecarboxylique.

5. L'utilisation selon la revendication 1, dans laquelle le composé est le sel de sodium ou de potassium de l'acide 2-(1,1'-biphényl-4-yl)-6-fluoro-3-méthyl-4-quinoléine carboxylique.

6. L'utilisation selon la revendication 1, dans laquelle le composé est le sel de sodium ou de potassium de l'acide 6-fluoro-3-méthyl-2-(4-phénoxyphényl)-4-quinoléine carboxylique.

7. L'utilisation selon la revendication 1, dans laquelle le composé est le sel de sodium ou de potassium de l'acide 2-(4'-bromo-1,1'-biphényl-4-yl)-6-fluoro-3-méthyl-4-quinoléine carboxylique.

8. L'utilisation selon la revendication 1, dans laquelle le composé est le sel de sodium ou de potassium de l'acide 2-(2'-fluoro-1,1'-biphényl-4-yl)-6-fluoro-3-méthyl-4-quinoléine carboxylique.

9. L'utilisation selon la revendication 1, dans laquelle le composé est combiné avec un médicament antiinflammatoire non stéroïde.

10. L'utilisation selon la revendication 4, dans laquelle le composé est combiné à un médicament antiinflammatoire non stéroïde.

11. L'utilisation selon la revendication 8, dans laquelle le composé est combiné à un médicament antiinflammatoire non stéroïde.